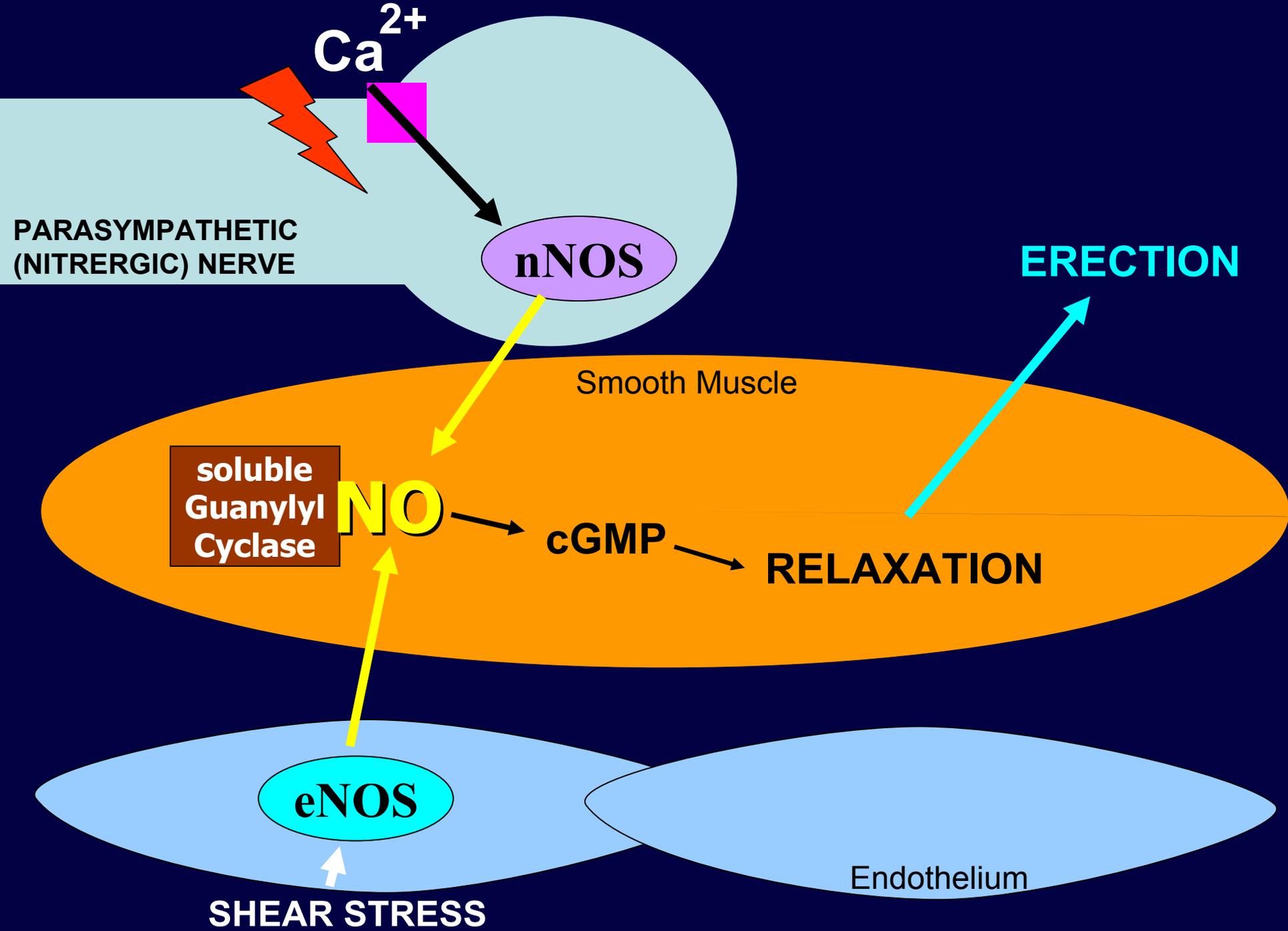


# Biphasic Nitroergic Degeneration: A new insight into diabetic autonomic neuropathy

**Selim Cellek**, MD, PhD

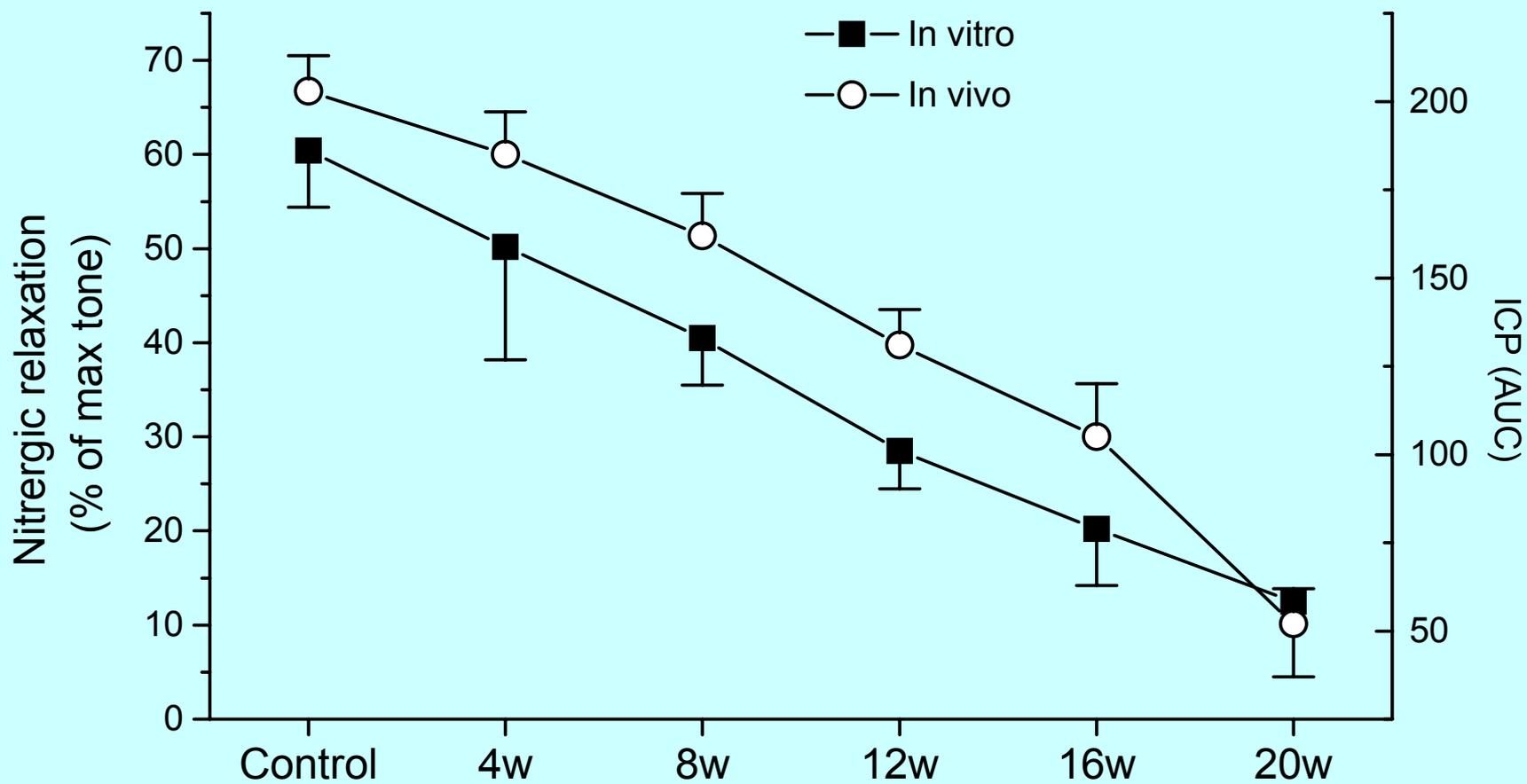
Wolfson Institute for Biomedical Research  
University College London  
LONDON, UK



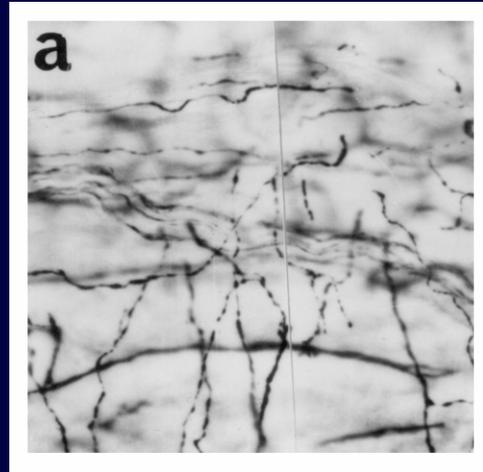


A clear deficiency of NO production within the penile autonomic nerves (nNOS) and endothelium (eNOS) has been demonstrated in diabetic patients and animal models.

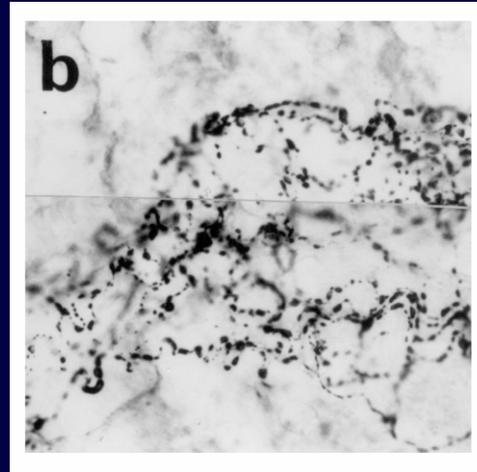
# Effect of diabetes on nitrenergic/ erectile responses *in vitro* and *in vivo*



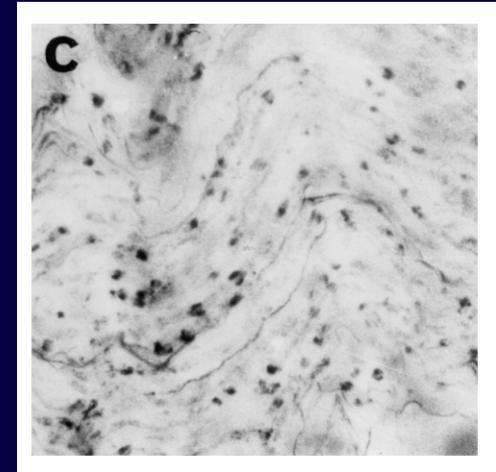
# Nitroergic Neurones In Diabetic Rat Penis



CONTROL

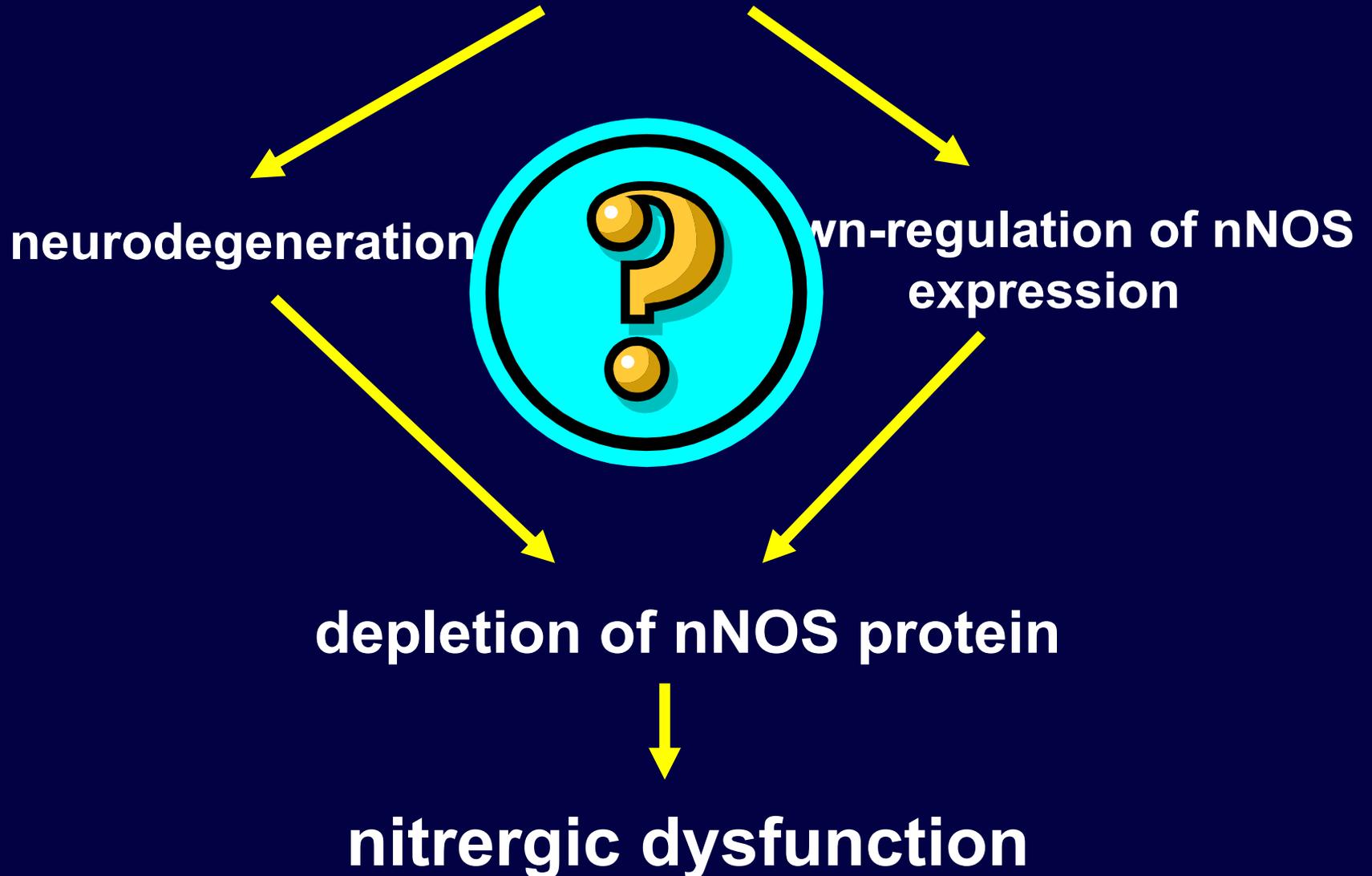


8w DIABETIC

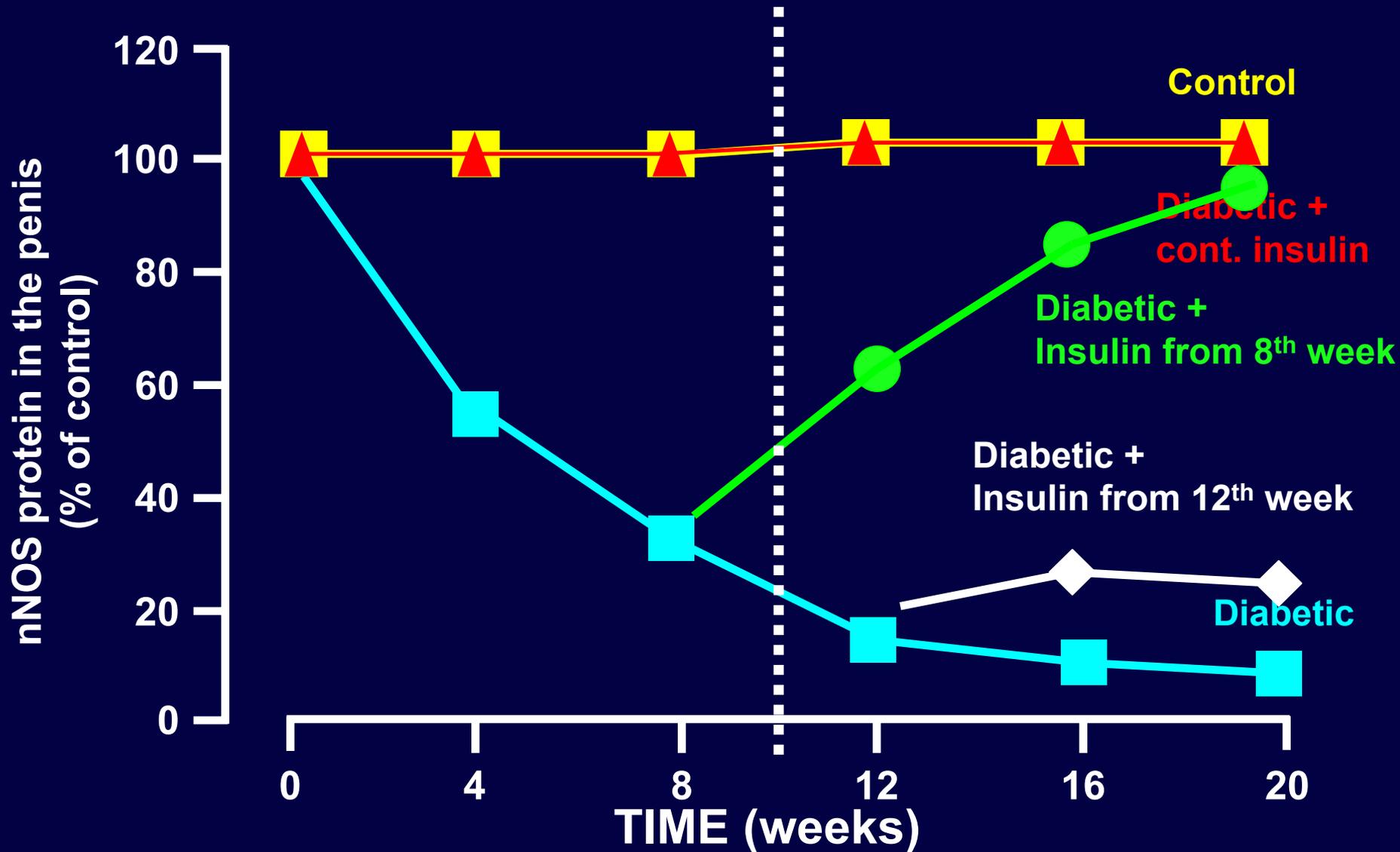


12w DIABETIC

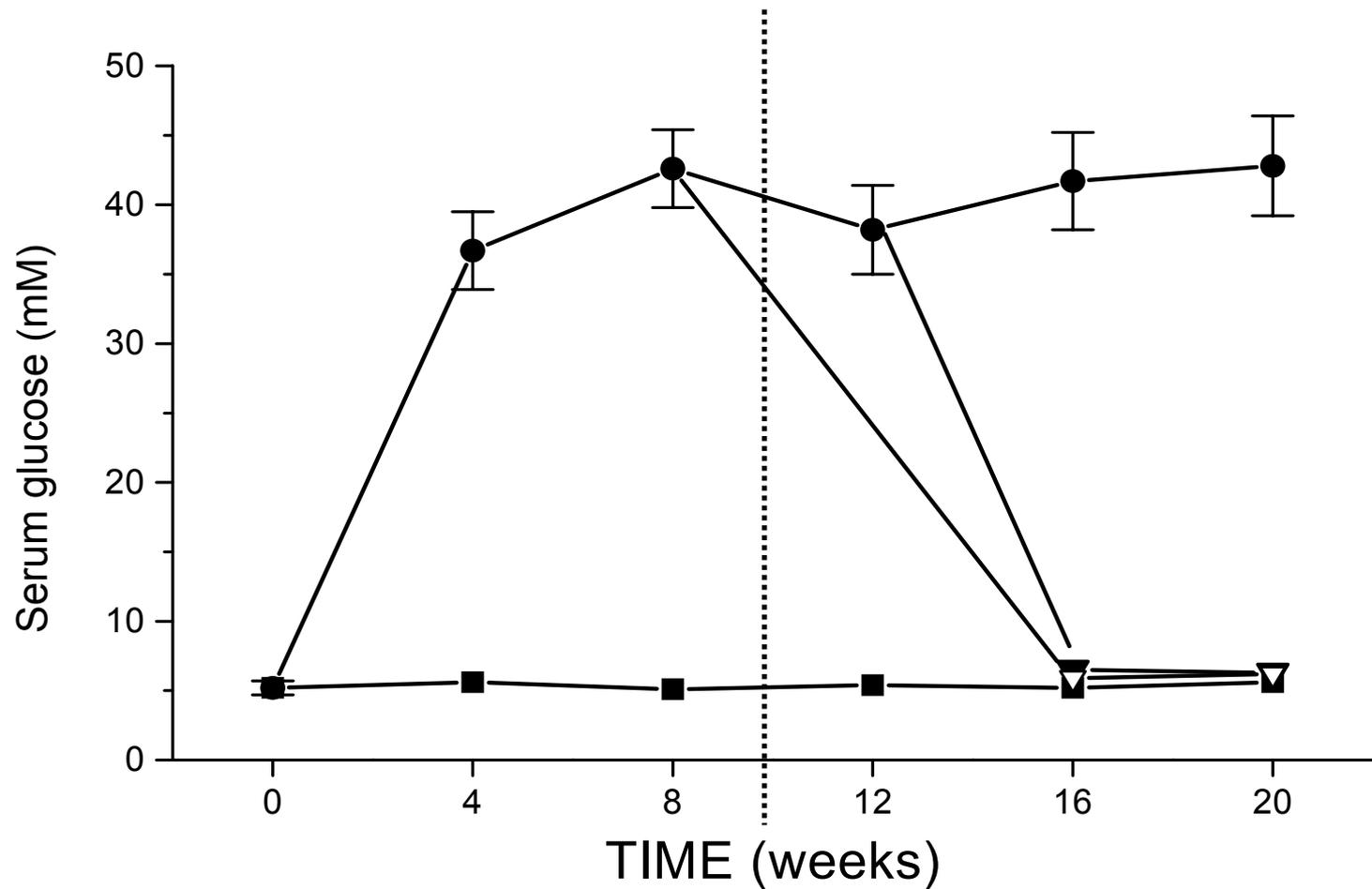
# DIABETES



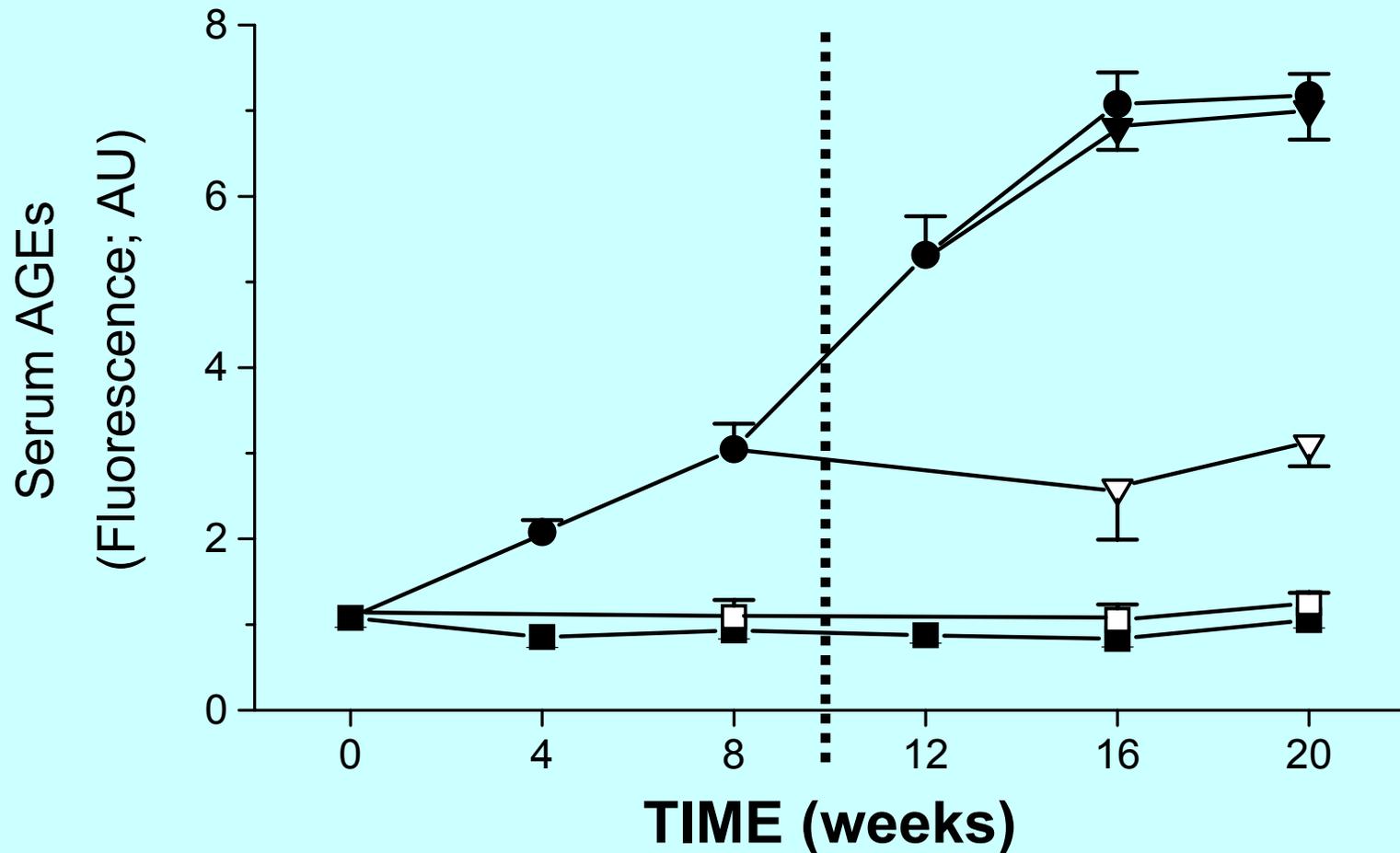
# Depletion of nNOS protein is irreversible after 12 weeks of diabetes



# Delayed insulin treatment normalises blood glucose levels



# Serum and tissue AGEs can not be reduced with insulin after a certain time point



# Diabetes mellitus

Axonal transport defect

nNOS depletion in the axons

Nitroergic dysfunction

AGEs accumulation

Oxidative stress

NO

Mitochondrial dysfunction

Caspase-3 activation

Apoptotic cell death

Nitroergic degeneration

AGEs

**POINT OF NO RETURN**

Reversible phase

Irreversible phase

# DIABETES

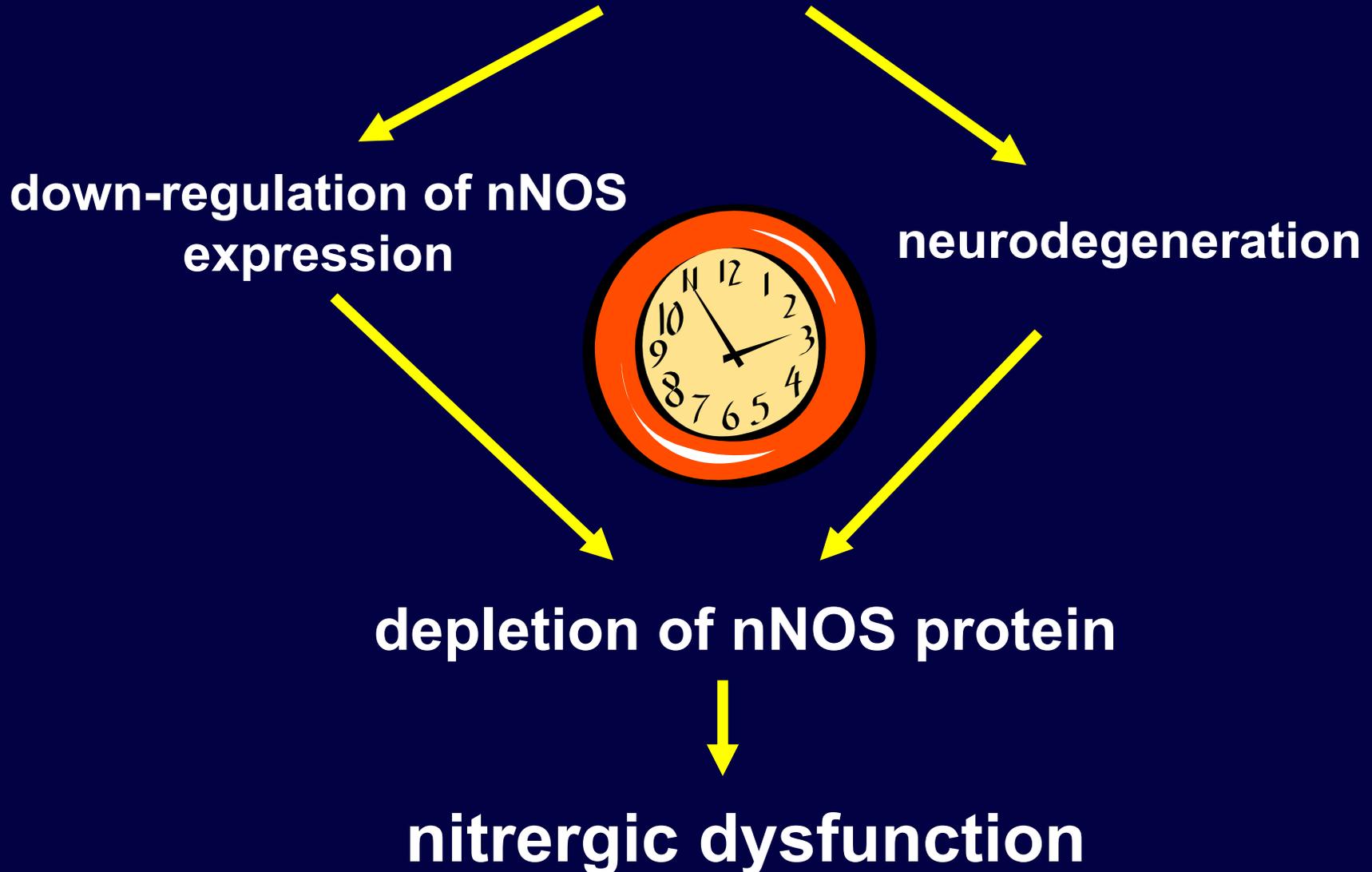
down-regulation of nNOS  
expression

neurodegeneration



depletion of nNOS protein

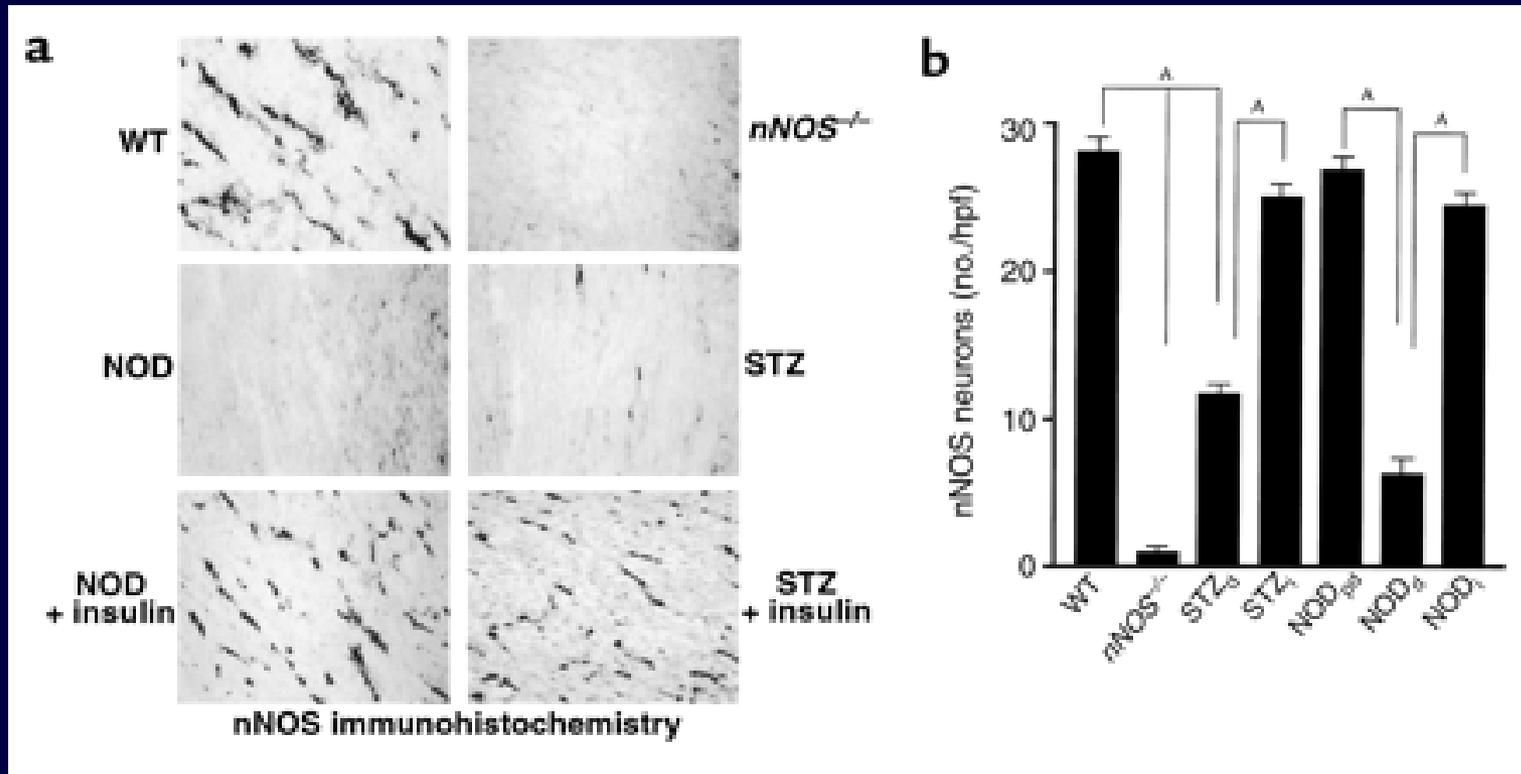
nitroergic dysfunction



## **A new insight into previous observations?**

- Reversal of nitrenergic dysfunction with insulin.

# Insulin treatment reverses nNOS depletion at 8 week STZ mice model

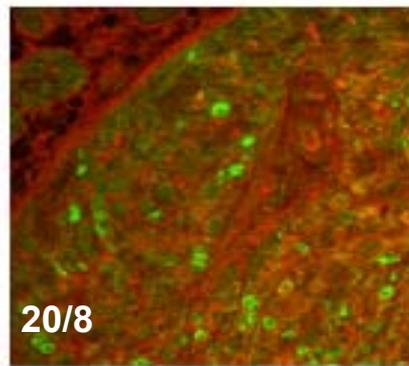
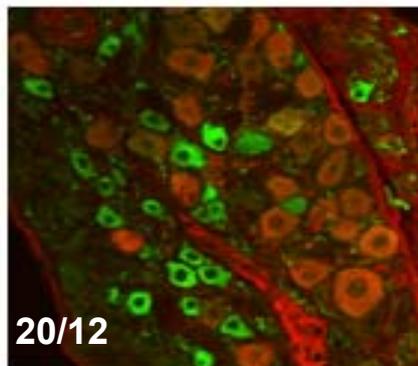
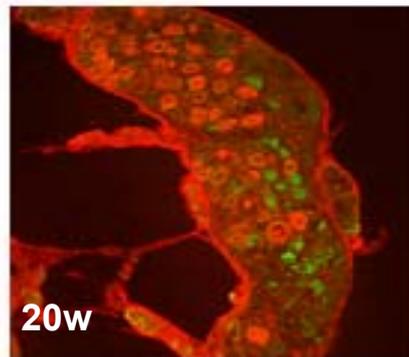
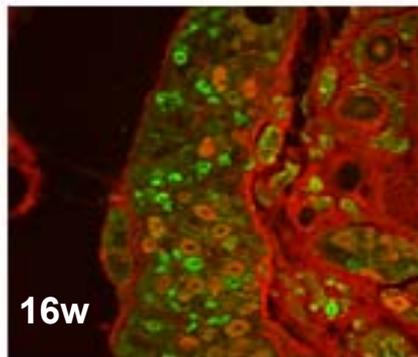
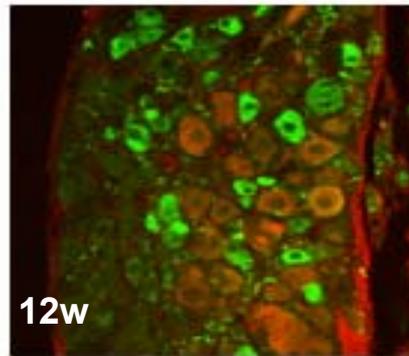
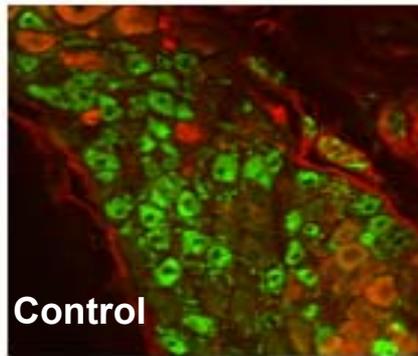


Watkins *et al*, J. Clin. Invest. 106: 373-384, 2000.

## **A new insight into previous observations?**

- Reversal of nitroergic dysfunction with insulin.
- Parasympathetic autonomic neuropathy develops before sympathetic autonomic neuropathy.

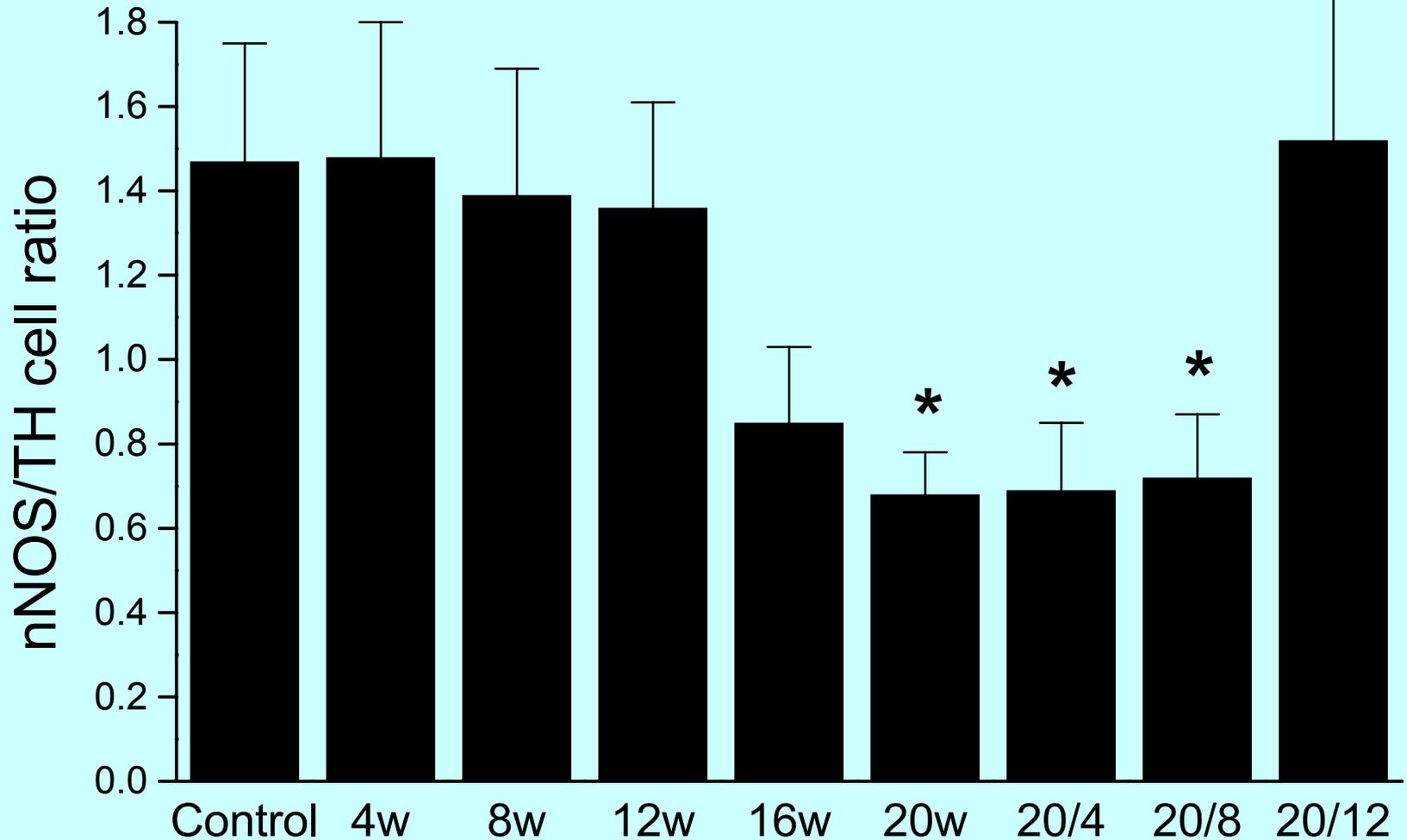
## nNOS vs TH



Degenerative process is specific to the nitrenergic cell bodies in the pelvic ganglia

Cellek *et al.*, Diabetes 52 (9) : 2353-2362, 2003.

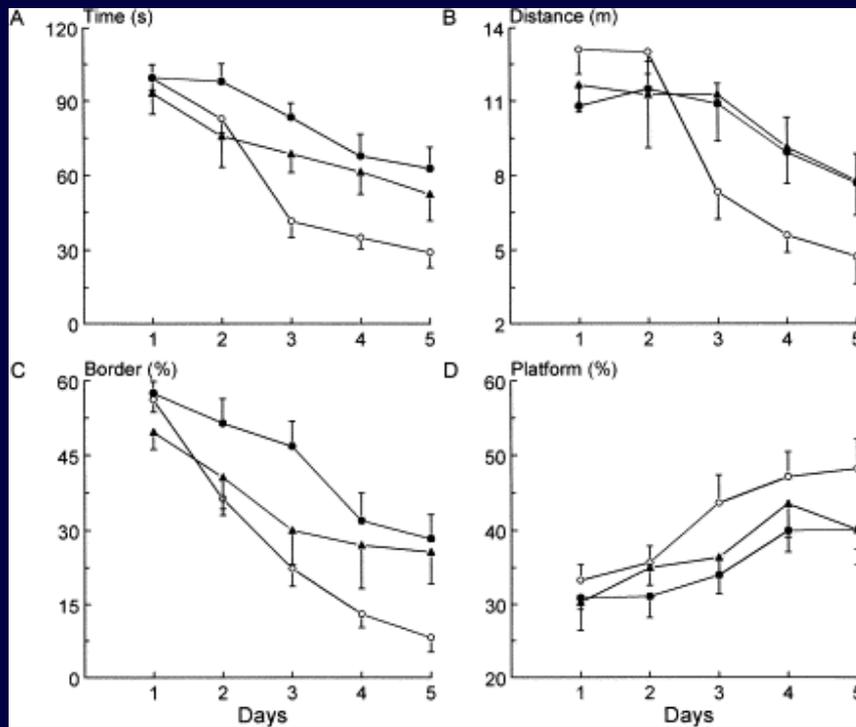
# Selective nitroergic degeneration leads to parasympathetic/sympathetic imbalance



## **A new insight into previous observations?**

- Reversal of nitroergic dysfunction with insulin.
- Parasympathetic autonomic neuropathy develops before sympathetic autonomic neuropathy.
- “Hyperglycemic memory” phenomenon (dogs develop retinopathy after 2.5 years high and 2.5 years normal glucose).
- Diabetes Control and Complications Trial (DCCT, 1993) 10 yrs, multicenter study: Intensive insulin therapy prevented development of complications in “primary intervention group” but not in “secondary intervention group”.
- Other organs which express NOS may be susceptible to damage in diabetes: CVS, kidneys, brain.

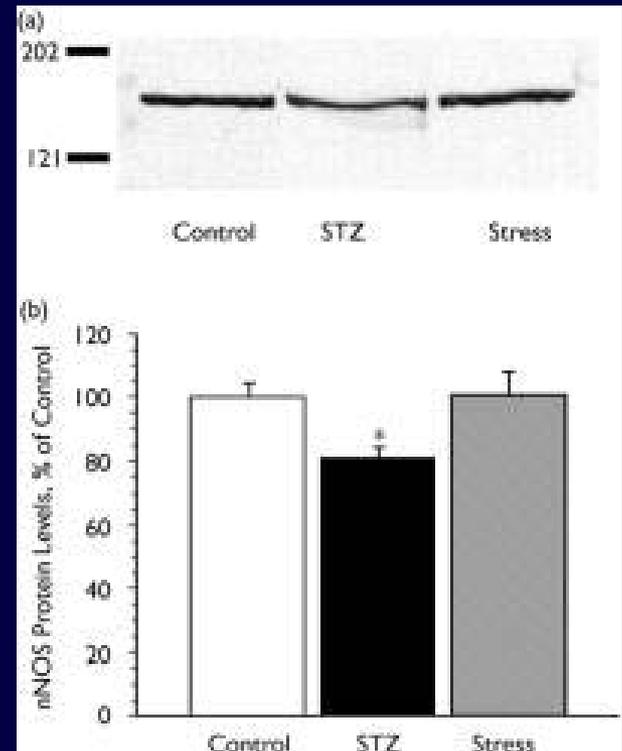
# Delayed insulin treatment does not reverse diabetes-induced learning deficiency and defect in LTP



Biessels *et al*,  
Brain Research 1998

# Diabetes causes nNOS depletion in rat hippocampus

## Rat hippocampus



Reagan & McEwen,  
NeuroReport 2002

# TREATMENT

- PDE5 inhibitors

- Inhibitors of AGE formation

- Anti-oxidants

POINT OF NO RETURN

- Drug targets which do not require endogenous NO:

  - Rho-kinase inhibitors

  - sGC activators

  - NO-releasing PDE5 inhibitors

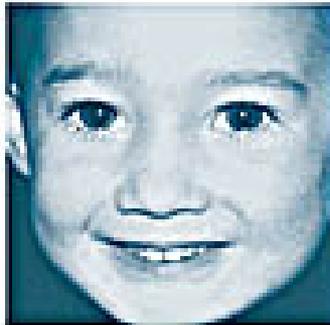
- AGE breakers (ALT compounds)

- AGE inhibitors (sRAGE)

- Stem cell therapy

- Gene therapy

**THANKS TO**



Juvenile  
Diabetes  
Research  
Foundation  
International

*dedicated to finding a cure*

**FOR THEIR CONTINUING SUPPORT**